

We claim:

~~1. A method of screening for a ligand analog, said method comprising the steps of:~~

- 5
- a) adding a candidate ligand to a non-naturally occurring cell surface receptor analog comprising an amino acid sequence that is less than about 95% identical to the extracellular domain of a corresponding naturally occurring human cell surface receptor, wherein said receptor analog binds a natural ligand for said naturally occurring human cell surface receptor at the same or higher binding affinity than said naturally occurring human cell surface receptor; and
 - b) determining the binding of said candidate ligand to said receptor analog.

10
2. A method according to claim 1, wherein said cell surface receptor analog is on the surface of a eukaryotic cell.

3. A method according to claim 1, wherein said cell surface receptor analog is on the surface of a prokaryotic cell.

15
4. A method according to claim 1, wherein said cell surface receptor analog is on the surface of a virus.

5. A method according to claim 1, wherein said cell surface receptor analog is immobilized on a solid support.

6. A method according to claim 1, wherein said cell surface receptor analog is in an aqueous solution.

20
7. A method according to claim 1, wherein said cell surface receptor analog comprises only an extracellular domain.

8. A method according to claim 1, wherein said cell surface receptor analog comprises an extracellular domain and a transmembrane domain.

9. A method according to claim 1, wherein said cell surface receptor analog comprises an extracellular domain, a transmembrane domain and a cytoplasmic domain.

10. A method according to claim 1, further comprising the steps of:

- 5
- c) designing said cell surface receptor analog, wherein said step of designing is executed by a computer program and wherein said cell surface receptor analog has a calculated structure that is different from a calculated structure of said corresponding naturally occurring human cell surface receptor;
 - d) synthesizing a nucleic acid encoding said cell surface receptor analog; and
 - e) expressing said cell surface receptor analog.

11. A method of screening for ligand analogs, said method comprising the steps of:

- 10
SUB
B₁
- a) providing a eukaryotic cell, comprising a non-naturally occurring cell surface receptor analog comprising an amino acid sequence that is less than about 95% identical to the extracellular domain of a corresponding naturally occurring human cell surface receptor, wherein said receptor analog binds a natural ligand for said naturally occurring human cell surface receptor at the same or higher binding affinity than said naturally occurring human cell surface receptor;
 - b) adding a candidate ligand to said eukaryotic cell; and
 - c) determining the signaling of said cell surface receptor analog.

12. A method according to claim 11, wherein said cell surface receptor analog is a chimeric receptor comprising an extracellular domain and a cytoplasmic domain from at least two different naturally occurring cell surface receptors.

13. A method according to claim 1 or 11, wherein said cell surface receptor analog comprises an exogenous dimerization domain.

14. A method according to claim 13, wherein said exogenous dimerization domain is fused to the cytoplasmic domain of said cell surface receptor analog.

15. A method according to claim 13, wherein said exogenous dimerization domain is fused to an internal site of said cell surface receptor analog.

16. A method according to claim 13, wherein said exogenous dimerization domain is fused to the extracellular domain of said cell surface receptor analog.

17. A method according to claim 1 or 11, wherein said naturally occurring human cell surface receptor is a cytokine receptor.

18. A method according to claim 1 or 11, wherein two monomers of said naturally occurring human cell surface receptor are crosslinked, whereby said non-naturally occurring cell surface receptor analog is formed.

19. A recombinant chimeric cell surface receptor complex, comprising at least two different monomers of a non-naturally occurring cell surface receptor analog wherein each of said monomers comprises an amino acid sequence that is different from an amino acid sequence of a corresponding naturally occurring human cell surface receptor, and wherein said recombinant chimeric cell surface receptor complex binds a natural ligand for said naturally occurring human cell surface receptor at the same or higher binding affinity than said naturally occurring human cell surface receptor.

add A'

add B²

add C²

add E'